Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration

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Abstract: PURPOSE: To report the efficacy and safety of intravitreal ranibizumab for neovascular age-related macular degeneration (nAMD) in real-world practice. METHODS: Metaanalysis of 26,360 patients from 42 real-world observational studies reporting outcomes of intravitreal ranibizumab for nAMD published between 2007 and 2015. Baseline demographics, lesion type, and visual acuity (VA) were recorded. The weighted mean was calculated for change in VA and frequency of injections and visits during year 1, year 2, and 3 years. Local and systemic adverse events were recorded. RESULTS: The mean change in VA for patients receiving a treat-and-extend regimen was +8.8 (95% confidence interval [CI]: 5.8 to 11.8), +6.7 (95% CI: 3.2 to 10.1), and +5.4 (95% CI: -4.1 to 14.9) Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 1 year (n = 1,539), 2 years (n = 2,521), and 3 years (n = 1,298), in comparison with +3.5 (95% CI: 2.0 to 5.0), +1.3 (95% CI: -1.6 to 4.2), and -1.9 (95% CI: -9.8 to 6.0) ETDRS letters for pro re nata at 1 year (n = 20,247), 2 years (n = 14,408), and 3 years (n = 11,714). Treat-and-extend patients received on average more injections (6.9 vs. 4.7) but had fewer visits (7.6 vs. 9.2) in the first year. Baseline characteristics were similar between the regimens. The reported rate of endophthalmitis was 17 of 66,176 intravitreal injections (0.026%). CONCLUSION: Intravitreal ranibizumab for nAMD prevents severe visual loss in real-world practice. Patients can achieve visual gain from baseline, but the extent to which these are maintained in the long term may depend on the frequency of injections.

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Review

METAANALYSIS OF REAL-WORLD OUTCOMES OF INTRAVITREAL RANIBIZUMAB FOR THE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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Purpose: To report the efficacy and safety of intravitreal ranibizumab for neovascular age-related macular degeneration (nAMD) in real-world practice.

Methods: Metaanalysis of ~26,360 patients from 42 real-world observational studies reporting outcomes of intravitreal ranibizumab for nAMD published between 2007 and 2015. Baseline demographics, lesion type, and visual acuity (VA) were recorded. The weighted mean was calculated for change in VA and frequency of injections and visits during year 1, year 2, and ≥3 years. Local and systemic adverse events were recorded.

Results: The mean change in VA for patients receiving a treat-and-extend regimen was +8.8 (95% confidence interval [CI]: 5.8 to 11.8), +6.7 (95% CI: 3.2 to 10.1), and +5.4 (95% CI: −4.1 to 14.9) Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 1 year (n = 1,539), 2 years (n = 2,521), and ≥3 years (n = 1,298), in comparison with +3.5 (95% CI: 2.0 to 5.0), +1.3 (95% CI: −1.6 to 4.2), and −1.9 (95% CI: −9.8 to 6.0) ETDRS letters for *pro re nata* at 1 year (n = 20,247), 2 years (n = 14,408), and ≥3 years (n = 11,714). Treat-and-extend patients received on average more injections (6.9 vs. 4.7) but had fewer visits (7.6 vs. 9.2) in the first year. Baseline characteristics were similar between the regimens. The reported rate of endophthalmitis was 17 of 66,176 intravitreal injections (0.026%).

Conclusion: Intravitreal ranibizumab for nAMD prevents severe visual loss in real-world practice. Patients can achieve visual gain from baseline, but the extent to which these are maintained in the long term may depend on the frequency of injections.

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Age-related macular degeneration is the leading cause of irreversible blindness in the developed world[1] and accounts for 5% of all blindness worldwide.[2] Humanized antibodies that inhibit vascular endothelial growth factor have been widely used clinically over the past decade after several randomized controlled trials demonstrated their benefit in improving visual outcomes in patients with neovascular age-related macular degeneration (nAMD).[3] However, there are several different treatment regimens for nAMD, including fixed dosing, *pro re nata* (PRN), and treat-and-extend.

Continuous monthly intravitreal ranibizumab therapy for nAMD was shown to be efficacious in the landmark MARINA[4] and ANCHOR[5] clinical trials. However, In real-world practice, many patients treated for nAMD do not meet the stringent inclusion criteria of these clinical trials. Also, monthly intravitreal injections pose a significant treatment burden for patients, carers, and healthcare providers. Therefore, discontinuous treatment regimens have become popular as they are more practical in the real-world setting. Discontinuous regimens include PRN, where patients are treated only when lesions are active, or "treat and extend," in which the interval between treatments is increased when the disease is stable with the aim of injecting just before the lesion is about to reactivate. Because of constraints in healthcare costs around the

world, different restrictions are placed on clinicians regarding frequency of treatments and patient visits.

The aim of this metaanalysis was to assess whether the impressive outcomes demonstrated from Phase 3 clinical trials translate to real-world clinical practice.[5] We paid particular attention to how visual acuity (VA) outcomes vary according to different treatment regimens across the world.

Methods

Search Strategy

A systematic search of the literature was conducted on May 1, 2015, using Medline, Embase, and Cochrane library databases. The fields searched by a multipurpose (.mp) search in Ovid databases generally looked in the Title, Original Title, Abstract, Subject Heading, Name of Substance, and Registry Word fields. The following search terms were used: *age related macular degeneration.mp* or *macular degeneration*; *AMD.mp*; *neovascular.mp*; *wet.mp* or *wet macular degeneration*; *vascular endothelial growth factors*; *visual acuity* or *visual outcomes*; *vision*; *ocular*; *blindness*; *registry.mp* or *registries*; *database.mp*; *long-term studies.mp*; *observation studies*; *phase IV study*. Further references were identified by manually searching included articles and consulting experts in the field.

Study Selection

Real-world studies of intravitreal ranibizumab therapy for nAMD published before the search date were included. Where possible, patients with at least one year follow-up were included. Randomized clinical trial results were excluded. Because there were no language exclusions in this metaanalysis, article abstracts were translated if required during the selection process and if included the full article was translated. The studies were grouped according to the region in the world where they were conducted, and then arranged with the most recent publication first.

Quality of Evidence

The selected studies are observational in nature and therefore provide low to moderate overall quality of evidence based on the Grading of Recommendations Assessment, Development and Evaluation classification.[6]

Data Extraction and Synthesis

The following data were extracted from each report:

1. Study design
2. Number of patients
3. Mean age of patients
4. Sex ratio
5. Baseline choroidal neovascularization (CNV) lesion type—predominantly classic, minimally classic (MC), occult, and other
6. Visual acuity at baseline, 1 year, 2 years, and ≥3 years after commencing anti–vascular endothelial growth factor treatment
7. Mean number of intravitreal injections administered per year
8. Total number of intravitreal injections administered
9. Mean number of visits per year
10. Treatment regimen and dosage
11. Total number of adverse events, specifically related to the ranibizumab therapy if specified
12. Number of cases of endophthalmitis, cerebrovascular accidents, and acute coronary syndromes
13. Number of deaths

The total number of patients enrolled across all studies was calculated as most studies reported the number of patients, rather than the number of eyes included. If a study only reported the number of eyes, it was assumed that one eye per patient was included. Studies were scrutinized to ensure that the patient population was analyzed once only where multiple studies on the same population were performed.

Visual acuity scores were converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letters for consistency, and approximate Snellen ratios were also noted.

Statistical Analysis

The weighted mean values for baseline age, sex ratio, CNV characteristics, VA, for yearly VA changes, the number of intravitreal injections, and patient visits per

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year were calculated across all studies. This was accomplished by weighting each study according to the proportion of patients it contributed to the metaanalysis.

To account for heterogeneity in outcome measures between studies, we also fit random-effects models to produce estimates for baseline age and VA, yearly VA changes, and the number of intravitreal injections and patient visits per year. Heterogeneity between studies was measured using the I^2 statistic to quantify the amount of inconsistency (i.e., heterogeneity), where I^2 values of 25%, 50%, and 75% indicate low, moderate, and substantial heterogeneity, respectively.[7] Mixed-effects models were also conducted using study region and treatment regimen as moderators to test as potential sources of heterogeneity and to provide estimates for yearly VA change and injections received by region and treatment regimen. The proportional reduction in variance was calculated to estimate the amount of heterogeneity that can be accounted for by the moderators, which can be thought of as a pseudo R^2 statistic.[8] When studies did not report the standard deviation, these values were imputed via multiple imputations and model results pooled.[9,10]

The ratio of injections to visits was calculated when these data were available.

When combined values were reported for MC and occult lesions, they were analyzed as part of the occult category. Otherwise, data on CNV characteristics that could not be separated into clinically relevant lesion types were excluded from this aspect of the analysis.

When the total number of intravitreal injections administered in a study was unavailable, it was calculated by multiplying the mean number of injections by the total number of patients in the study.

Analyses were conducted using R version 3.2.3 and the *mice* (for multiple imputations) and *metafor* (for random- and mixed-effects models) packages.[8,11,12]

Results

Included Studies

The literature search returned a total of 613 articles. Based on our inclusion and exclusion criteria, 42 articles published between 2007 and May 2015 were included. There were a total of 45,381 patients with nAMD across all the studies included. However, taking into account multiple studies that were based on the same patient population, ~26,360 different patients were included.

Summary Tables

The patient demographics in these studies are summarized in Table 1, with the corresponding VA data and treatment regimens listed in Table 2. The safety outcomes of each study are presented in Table 3. Table 4 summarizes the weighted outcome means and overall outcomes measures as estimated by random-effects models, regional and treatment regimen outcome measures as estimated by mixed-effects models, and an assessment of heterogeneity.

Baseline Characteristics

The mean age of patients across all studies was 78.8 years (95% confidence interval [CI]: 78.0 to 79.5) and 63.3% were female. There was a wide range in the mean baseline VA across studies (36.5–75.0 ETDRS letters; 6/60 to 6/9.5 Snellen approximate). The mean baseline VA for the pooled data was 53.6 ETDRS letters (6/24 Snellen approximate).

Patients treated under PRN regimens had a mean age of 78.5 years and mean baseline VA of 53.0 ETDRS letters (6/24 Snellen approximate). For patients under treat-and-extend regimens, their mean age was 79.0 years and their mean baseline VA was 52.0 ETDRS letters (6/24 Snellen approximate). Females accounted for 63.4% and 62.2% of patients in PRN and treat-and-extend regimens, respectively. The mean baseline VA for studies from Europe, United Kingdom, and Australia were 56.0, 53.6, 46.6, and 57.5 ETDRS letters, respectively, (6/24, 6/24, 6/38, and 6/19 Snellen approximates, respectively).

Of the 9,350 patients with data available on their CNV lesion, the majority had an occult lesion (50.2%), followed by predominantly classic (21.1%), unclassified (17.5%), MC (8.1%), and others including retinal angiomatous proliferation (3.1%). This distribution was similar for both PRN and treat-and-extend regimens. Holz et al[13] also reported that 11.7% (n = 199) of their patients had both occult and classic lesions. Heimes et al[14] and Pushpoth et al[15] reported the combined number of patients with either predominantly or MC lesions. These two values could not be separated and were therefore excluded from the analysis of lesion type. Pushpoth et al,[15] Katz et al,[16] and Abedi et al[17] reported the combined number of patients with MC or occult lesions, and these were included into the occult category for analysis.

For comparison, the baseline characteristics of the MARINA and ANCHOR clinical trials using 0.5-mg ranibizumab were mean baseline best-corrected VA of 53.7 and 47.1 ETDRS letters (6/24 and 6/38 Snellen approximates), mean age of 77.0 and 76.0 years, and the mean percentage of females 63.3% and 46.4%, respectively.

Visual Acuity Outcomes

Overall, there was a mean change of +5.0 (95% CI: 3.4 to 6.6), +3.4 (95% CI: 0.9 to 5.8), and +1.1 (95%

Table 1. Demographic Information of the Patients in the Included Studies

Article	Patients (n)	Mean Age (Years)	Female (%)	Baseline CNV (%)				Study Type
				PC	MC	Occult	Other	
International								
Holz et al[13]	2,227	76.9	60.6	27.7	—	40.6	0.5	Retrospective
Germany	420	76.7	59.8	—	—	—	—	—
France	398	77.5	60.6	—	—	—	—	—
United Kingdom	410	77.7	60.2	—	—	—	—	—
Italy	365	75.2	58.1	—	—	—	—	—
Netherlands	350	77.2	62.9	—	—	—	—	—
Canada	188	79.8	60.6	—	—	—	—	—
Ireland	49	72.7	73.5	—	—	—	—	—
Venezuela	47	73.1	59.6	—	—	—	—	—
Silva et al[21]	210	75.7	56.8	—	—	—	—	Phase 4 extension study
Continental Europe								
Souied et al[22]	881	79.0	68.0	27.8	11.0	61.3	—	Retrospective
van Asten et al[23]	231	77.9	58.9	17.7	16.9	61.9	3.5	Prospective
Frennesson and Nilsson[24]	268	78.9	66.8	19.2	11.2	43.9	25.6	Retrospective
Mantel et al[25]	104*	79.5	63.5	24.4	10.4	45.2	20.0	Prospective
Menghini et al[26]	194	79.3	63.2	17.2	12.3	70.5	—	Retrospective
Wolf and Kampik[27]	1,729	77.8	63.2	24.4	7.8	41.3	—	Prospective
Cohen et al[28]	551	78.2	63.2	33.3	12.0	54.7	—	Retrospective
Falk et al[29]	855	77.3	62.8	—		—	—	Retrospective
Finger et al[30]	3,470	≤65 (5.6%) 66–80 (51.3%) >80 (42.3%)	64.6	24.5	11.6	63.9	—	—
Holz et al[31]	4,444	—	—	—	—	—	—	Retrospective
Germany	3,470	77.6	64.6	—	—	—	—	—
Netherlands	243	77.9	59.3	—	—	—	—	—
Belgium	260	78.7	62.1	—	—	—	—	—
Sweden	471	78.1	66.0	—	—	—	—	—
Rakic et al[32]	267	78.5	62.4	18.0	8.2	60.4	34.2	Prospective
Biarnés et al[33]	67	77.8	80.0	13.0	11.0	34.0	—	Retrospective
Heimes et al[14]	145	77.1	70.3	15.1	84.8	—	Retrospective	
Hjelmqvist et al[19]	370	77.7	66.8	—	—	—	—	Prospective and retrospective
Oubraham et al[34]	—	—	—	—	—	—	—	Retrospective
PRN	52	79.1	53.0	26.9	—	63.0	9.6	
Treat and extend	38	79.1	65.0	15.8	—	84.0	—	
Querques et al[35]	79	77.17	58.3	8.3	15.6	76.0		Retrospective
Cohen et al[36]	122	78.3	70.0	25.0	—	75.0	—	—
Rothenbuehler et al[37]	138	76.5	64.0	31.0	4.0	65.0	—	Prospective

(*continued on next page*)

Table 1. (*Continued*)

Article	Patients (n)	Mean Age (Years)	Female (%)	Baseline CNV (%)				Study Type
				PC	MC	Occult	Other	
United Kingdom								
Writing Committee for the U.K. Age-Related Macular Degeneration E. M. R. Users Group[38]	11,135	79.7	63.0	—	—	—	—	Retrospective
Zarranz-Ventura et al[39]	11,135	79.0	63.5	—	—	—	—	—
Muniraju et al[40]	156	82.7	66.0	—	—	—	—	Retrospective
Pushpoth et al[15]	1,017*	75.0	—	28.6	59.76	11.69	Retrospective	
Rotsos et al[41]	50	80.0	60.0	10.0	—	90.0	—	Retrospective
North America								
Rayess et al[42]	196†	80.3	65.1	—	—	—	—	Retrospective, interventional, consecutive case series
Rofagha et al[43]	155	—	—	31.0	25.0	45.0	—	Cross-sectional cohort study
Bellerive et al[44]	45	76.9	71.0	38.0	34.0	18.0	2.0	Retrospective
Katz et al[16]	56	—	—	—	—	—	—	Retrospective
Monthly	28*	80.8	Not reported	19.0	—	77.0	3.0	
PRN	28*	78.5	Not reported	10.0	—	90.0	0	
Bandukwala et al[45]	94	81.0	63.0	16.0	16.0	26.0	—	Retrospective
Engelbert et al[46]	16†	79.0	75.0	—	—	—	16	Retrospective
Gupta et al[20]	92*	80.6	66.3	19.6	28.7	52.2	—	Retrospective
Dadgostar et al[47]	124*	81.3	64.5	16.3	16.3	66.3	—	Retrospective
Australia								
Barthelmes et al[48]	655	79.4	61.4	16.8	17.3	46.0	6.0	Retrospective
Gillies et al[49]	1,007*,†	79.5	65.8	16.4	15.5	55.8	4.0	Database observational study
Abedi et al[17]	120†	77.7	59.2	27.5	—	72.5	—	Prospective cohort study
Arnold et al[50]	1,011	79.4	61.3	15.9	18.1	50.1	4.3	Database observational study
Barthelmes et al[51]	176	78.6	62.0	—	—	—	—	Retrospective
Gillies et al[52]	646*	79.2	61.9	—	30.5	69.5	—	Database observational study
Gillies et al[53]	850*†	79.3	61.3	48.4	21.4	53.6	7.7	Prospective
Toalster et al[54]	45	81.7	64.0	—	24.4	44.4	—	Prospective
Michalova et al[18]	158*	80	73.4	23.0	17.0	60.0	—	Retrospective

*Completely or mostly treatment naive.
†Includes some patients who received bevacizumab.
PC, predominantly classic.

Table 2. Visual Acuity and Treatment Regimen Data in the Included Studies

Article	Change in VA (ETDRS Letters)				Mean No. Injections	Mean No. Visits	Treatment Regimen
	Baseline Nearest Snellen Score Written Within Brackets	1 yr	2 yr	≥3 yr			
International							
Holz et al[13]	55.4 (6/24)	+2.4	+0.6	—	3.6	6.8	Not reported
Germany	52.9 (6/30)	+1.1	−0.8	—	2.8	5.4	(PRN)
France	56.0 (6/24)	+0.8	−1.1	—	3.2	6.7	(PRN)
United Kingdom	55.0 (6/24)	+6.0	+4.1	—	4.5	9.2	(PRN)
Italy	65.5 (6/15)	0.0	−2.9	—	2.6	3.3	
Netherlands	50.1 (6/30)	+3.8	+2.6	—	4.3	6.4	
Canada	47.2 (6/38)	+3.2	+1.6	—	5.0	6.9	
Ireland	64.7 (6/15)	+2.3	+3.3	—	5.5	6.8	
Venezuela	48.3 (6/30)	+2.6	+1.4	—	1.6	4.2	
Silva et al[21]	60.7 (6/19)	—	−4.3	—	3.1	Not reported	PRN
Continental Europe							
Souied et al[22]	56.8 (6/24)	+4.3	—	—	5.6	7.4	Loading and PRN (4.1%) PRN (6.5%) monthly (0.1%)
van Asten et al[23]	45.1 (6/38)	+5.6	+3.4	—	6.7	Not reported	Loading and PRN
Frennesson and Nilsson[24]	58.4 (6/19)	+1.8	+1.0	+0.1	3.4	10.6	Loading and PRN
Mantel et al[25]	58.3 (6/19)	+9.8	—	—	7.8	4.0	Loading and PRN
Menghini et al[26]	55.2 (6/24)	+5.0	+1.5	—	4.5	9.7	Loading and PRN (28.4%)
PRN							
Wolf and Kampik[27]	75.0* (6/9.5)	+0.4*	—	—	4.5	Not reported	Loading and PRN
Cohen et al[28]	53.2 (6/24)	+3.2	—	—	5.1	8.6	Loading and PRN
Falk et al[39]	53.2 (6/24)	—	50.5	—	4.4	Not reported	Loading and PRN
Finger et al[30]	49* (6/30)	−1.0*	—	—	4.3	Not reported	Loading and PRN
Holz et al[31]	—	—	—	—	—	—	—
Germany	48.8 (6/30)	−0.8	—	—	4.0	Not reported	Loading and PRN
Netherlands	45.1 (6/38)	+5.6	—	—	5.1	Not reported	—
Belgium	56.3 (6/24)	+2.5	—	—	5.0	Not reported	—
Sweden	58.3 (6/19)	+1.0	—	—	4.4	Not reported	—
Rakic et al[32]	56.3 (6/24)	+1.6	−2.4	—	3.8	Not reported	Loading and PRN
Biarnés et al[33]	57.8 (6/19)	+1.3	—	—	3.5	Not reported	PRN
Heimes et al[14]	54.5* (6/24)	−1.0*	—	—	4.98	Not reported	Loading and PRN
Hjelmqvist et al[19]	58.3 (6/19)	+1.0	—	—	4.7	10.3	Loading and PRN
Oubraham et al[34]	—	—	—	—	—	—	—
PRN	59.4 (6/19)	+2.3	—	—	5.2	8.8	PRN
Treat and extend	61.2 (6/19)	+10.8	—	—	7.8	8.5	Treat and extend
Querques et al[35]	46* (6/38)	+9.0	+7.0	—	—	Not reported	Loading and PRN
Cohen et al[36]	56.15 (6/24)	+0.7	—	—	3.79	8.07	Loading and PRN
Rothenbuehler et al[37]	49.7 (6/30)	+7.3	+6.3	—	5.0	Not reported	PRN
United Kingdom							

(*continued on next page*)

Table 2. (*Continued*)

Article	Change in VA (ETDRS Letters)				Mean No. Injections	Mean No. Visits	Treatment Regimen
	Baseline Nearest Snellen Score Written Within Brackets	1 yr	2 yr	≥3 yr			
Writing Committee for the U.K. Age-Related Macular Degeneration E. M. R. Users Group[38]	55 (6/24)	+2	+1	−2	4.3	8.5	Loading and PRN
Zarranz-Ventura et al[39]	—	—	—	—	—	—	Loading and PRN
First eye	52* (6/30)	—	0*	+0.5*	4.4	8.1	
Second eye	64.5* (6/15)	—	−3.5*	−7.5*	4.3	9.1	
Muniraju et al[40]	48.2 (6/30)	+3.0	+2.2	+0.9	3.4	Not reported	Loading and PRN
Pushpoth et al[15]	—	—	—	—	3.74	Not reported	Treat and extend
Pretreatment	50.43 (6/30)	+2.7	+0.9	−0.42			
No pretreatment	54.09 (6/24)	+3.8	+2.4	+0.23			
Rotsos et al[41]	46 (6/38)	+4.6	—	—	4.7	11	Loading and PRN
North America							
Rayess et al[42]	43* (20/136)	+11.6	+10.7*	+13.6*	6.4	6.4	Treat and extend
Rofagha et al[43]	54.3 (6/24)	—	—	−6.9	2.0	—	Monthly and PRN
Bellerive et al[44]	50.5* (6/30)	+7.0*	—	—	4.92	—	Loading and PRN
Katz et al[16]	—	—	—	—	—	—	—
Monthly	37.5* (6/60)	+13	—	—	12	13	Monthly
PRN	36.5* (6/60)	+10	—	—	8	11	Loading and PRN
Bandukwala et al[45]	52.5 (6/24)	+2.9	—	—	5.1	9.4	—
Engelbert et al[46]	58* (6/19)	—	+1*	+1*	10	10	Treat and extend
Gupta et al[20]	43* (6/38)	+13*	+11*	—	7.45	7.93	Treat and extend
Dadgostar et al[47]	49* (6/30)	+2.0*	—	—	5.2	—	PRN
Australia							
Barthelmes et al[48]	—	—	—	—	—	—	Treat and extend and PRN (20%)
Low	55.8 (6/24)	+6.8	—	—	7.6	—	
Moderate	53.7 (6/24)	+8.3	—	—	7.9	—	
High	54.0 (6/24)	+6.2	—	—	8.4	—	
Persistent	54.0 (6/24)	+5.5	—	—	8.3	—	
Gillies et al[49]	55.3 (6/24)	+5.5	—	—	4.2	Not reported	—
Abedi et al[17]	51.2 (6/30)	+9.5	+8.0	—	7.1	7.1	Loading and Treat and extend
Arnold et al[50]	56.5 (6/24)	—	+5.3	—	6.5	7.4	Treat and extend
Barthelmes et al[51]	—	—	—	—	—	—	—
First eye	49.7 (6/30)	+7.2	—	—	6.3	Not reported	—
Second eye	61.2 (6/19)	+3.8	—	—	7.3	Not reported	—
Gillies et al[52]	55 (6/24)	+4.9	—	—	7.3	9.5	Treat and extend (74%) PRN and monthly (22%) Monthly (4%)
Gillies et al[53]	57.1 (6/24)	+4.7	—	—	7.0	—	—
Toalster et al[54]	61.0* (6/19)	+6.0*	—	—	8.0	7.0	Loading and Treat and extend
Michalova et al[18]	62.0* (6/19)	+7.0*	—	—	9.2	—	—

*Converted to ETDRS letters.

Table 3. Ocular and Systemic Safety Outcomes of Each Included Study

Article	Total No. Adverse Events	Ocular (Endophthalmitis)	Systemic (CVA, ACS)	Deaths
International				
Holz et al[13]	5*	4*	Not reported	1*†
Silva et al[21]	359	2	1	5†
Continental Europe				
van Asten et al[23]	64‡	Not reported	3	18
Frennesson and Nilsson[24]	65	Not reported	3	26
Mantel et al[25]	0	0	0	0
Wolf and Kampik[6]	37	Unable to be calculated	Unable to be calculated	Unable to be calculated
Finger et al[27]	505	51§	6§	42†
Holz et al[31]	128	5	29	Not reported
Germany	84	4	23	Not reported
the Netherlands	22	0	2	Not reported
Belgium	18	1	2	Not reported
Sweden	4	0	2	Not reported
Rakic et al[32]	155	13	6	5
Hjelmqvist et al[19]	16	0	3	4
Querques et al[35]	0	0	0	0
Rothenbuehler et al[37]	0	0	0	0
United Kingdom				
Rotsos et al[41]	0	0	0	0
North America				
Bellerive et al[44]	Unable to be calculated	0	0	0
Engelbert et al[46]	0	0	0	0
Gupta et al[20]	0	0	0	0
Australia				
Barthelmes et al[48]	9	4	Not reported	Not reported
Abedi et al[17]	9	4	2	4
Arnold et al[50]	35	2	Not reported	Not reported
Gillies et al[53]	82	2	Not reported	Not reported
Toalster et al[54]	0	0	0	0
Michalova et al[18]	10	0	6	0

*Value had to be calculated.
†Deaths separate to reported adverse events.
‡Adverse events not related to the ranibizumab treatment.
§Adverse events related to the ranibizumab treatment.
ACS, acute coronary syndrome; CVA, cerebrovascular accident.

CI: −5.3 to 7.5) ETDRS letters at 1 year (n = 24,039), 2 years (n = 17,928), and ≥3 years (n = 13,012), respectively. There was a regional difference in VA change at 1 year, with a gain of +3.1 (95% CI: 1.2 to 5.0), +2.5 (95% CI: 1.3 to 3.8), +6.0 (95% CI: 3.2 to 8.7), and +7.7 (95% CI: 3.0 to 12.4) ETDRS letters in continental Europe (n = 9,988), United Kingdom (n = 12,886), North America (n = 795), and Australia (n = 323), respectively.

Data were extracted for treat-and-extend and PRN regimens where it was specified, as shown in Table 2. For studies based purely on PRN regimens (n = 21,612), the mean VA change was +3.5 (95% CI: 2.0 to 5.0), +1.3 (95% CI: −1.6 to 4.2), and −1.9 (95% CI: −9.8 to 6.0) ETDRS letters at 1 year (n = 20,247), 2 years (n = 14,408), and ≥3 years (n = 11,714), respectively. In contrast, patients of studies based solely on treat-and-extend regimens (n = 2,566) had a mean VA change of +8.8 (95% CI: 5.8 to 11.8), +6.7 (95% CI: 3.2 to 10.1), and +5.4 (95% CI: −4.1 to 14.9) ETDRS letters at 1 year (n = 1,539), 2 years (n = 2,521), and ≥3 years (n = 1,298) respectively. Patients receiving a treat-and-extend regimen achieved significantly better outcomes at 1 and 2 years ($P < 0.001$ and $P = 0.021$ respectively; mixed-effects models) compared with patients on PRN. This difference was not significant at ≥3 years ($P = 0.168$; mixed-effects models).

Most patients had a baseline VA between 35 and 55 ETDRS letters (n = 17,464; 6/60 to 6/24 Snellen

Table 4. Weighted Outcome Means and Overall Outcome Measures as Estimated by Random-Effects Models, and Regional and Treatment Regimen Outcome Measures as Estimated by Mixed-Effects Models

Variable	Weighted Mean	Random-Effects Estimate (95% CI)	I^2 (%)	Moderator R^2 (%)	
				Region	Regimen
Baseline age					
Overall	78.6	78.8 (78.0 to 79.5)	96.5	25.1	0.0
PRN	78.3	78.5 (77.6 to 79.4)			
T&E	77.7	79.0 (77.4 to 80.6)			
Baseline VA					
Overall	55.3	53.6 (51.0 to 56.2)	98.9	22.5	0.0
Europe	56.5	56.0 (53.3 to 58.7)			
United Kingdom	54.8	53.6 (50.6 to 56.7)			
United States	47.4	46.6 (43.5 to 49.7)			
Australia	57.8	57.5 (51.2 to 63.9)			
PRN	55.4	53.0 (50.0 to 56.0)			
T&E	53.5	52.0 (46.5 to 57.6)			
ΔVA 1 year					
Overall	+2.1	+5.0 (3.4 to 6.6)	97.9	0.0	34.1
Europe	+1.2	+3.1 (1.2 to 5.0)			
United Kingdom	+2.3	+2.5 (1.3 to 3.8)			
North America	+7.0	+6.0 (3.2 to 8.7)			
Australia	+7.8	+7.7 (3.0 to 12.4)			
PRN	+1.7	+3.5 (2.0 to 5.0)			
T&E	+5.7	+8.8 (5.8 to 11.8)			
ΔVA 2 year					
Overall	+1.3	+3.4 (0.9 to 5.8)	97.7	13.3	30.4
PRN	+0.8	+1.3 (−1.6 to 4.2)			
T&E	+4.7	+6.7 (3.2 to 10.1)			
ΔVA ≥3 years					
Overall	−1.6	+1.1 (−5.3 to 7.5)	98.5	0.0	26.0
PRN	−2.0	−1.9 (−9.8 to 6.0)			
T&E	+2.2	+5.4 (−4.1 to 14.9)			
Mean yearly injections					
Overall	4.4	5.4 (4.6 to 6.2)	99.8	24.5	31.5
Europe	4.3	4.3 (3.5 to 5.1)			
United Kingdom	5.0	5.6 (4.8 to 6.4)			
North America	6.2	6.1 (5.3 to 6.9)			
Australia	7.8	7.7 (5.9 to 9.5)			
PRN	4.3	4.7 (4.0 to 5.5)			
T&E	5.2	6.9 (5.6 to 8.2)			
Mean injections year 1					
Overall	5.0	6.3 (5.2 to 7.5)	99.7	—	44.1
PRN	5.2	5.4 (4.1 to 6.8)			
T&E	6.6	7.3 (5.9 to 8.6)			
Mean injections year 2					
Overall	3.8	4.4 (3.2 to 5.6)	99.3	—	15.8
PRN	3.4	3.7 (1.8 to 5.5)			
T&E	4.5	4.9 (3.3 to 6.5)			
Mean injections year 3					
Overall	3.8	3.3 (1.1 to 5.6)	99.5	—	0.0
PRN	3.6	2.8 (0.0 to 6.8)			
T&E	3.2	4.0 (0.0 to 8.9)			
Mean number of visits					
Overall	7.8	8.3 (7.2 to 9.4)	99.8	0.0	5.7
PRN	7.8	8.8 (7.4 to 10.3)			
T&E	7.3	7.6 (5.9 to 9.3)			
Mean visits year 1					
Overall	9.0	8.4 (7.1 to 9.7)	99.8	—	4.1
PRN	9.0	8.6 (6.8 to 10.3)			
T&E	7.6	7.8 (5.5 to 10.1)			

Table 4. (*Continued*)

Variable	Weighted Mean	Random-Effects Estimate (95% CI)	I^2 (%)	Moderator R^2 (%)	
				Region	Regimen
Mean visits year 2					
Overall	7.7	7.7 (5.5 to 9.8)	99.8	—	3.2
PRN	7.9	9.2 (4.4 to 14.0)			
T&E	6.5	7.6 (4.6 to 10.7)			
Mean visits year 3					
Overall	8.2	7.3 (4.9 to 9.8)	96.6	—	2.3
PRN	8.3	8.2 (0.0 to 17.5)			
T&E	6.4	7.0 (1.2 to 12.8)			

Amount of heterogeneity between studies is given by I^2 and the amount that is explained by moderators study region and treatment regimen in mixed-effects models is given R^2 where applicable.

equivalent). This was followed by the 55 to 70 ETDRS letters group (n = 4,675; 6/24 to 6/12 Snellen equivalent) and those with VA >70 ETDRS letters (n = 1,729; >6/12 Snellen equivalent). Patients who commenced treatment with better baseline VA maintained better VA up to at least 36 months (Figure 1).

The mean change in VA in the first year of treatment generally increased with the mean number of injections that were administered that year (Figure 2).

Treatment Burden

The patients collectively received a mean number of 5.4 injections (95% CI: 4.6 to 6.2) and 8.3 visits (95% CI: 7.1 to 9.7) per year. There were more injections and visits in the first year—with patients receiving a mean of 6.3 injections (n = 25,024; 95% CI: 5.2 to 7.5) and 8.4 visits (n = 15,559; 95% CI: 7.1 to 9.7). In the second year, there were 4.4 injections (n = 17,704; 95% CI: 3.2 to 5.6) and 7.7 visits (n = 13,980; 95% CI: 5.5 to 9.8). For subsequent years, there was an annual mean of 3.3 injections (n = 13,104; 95% CI: 1.1 to 5.6) and 7.3 visits (n = 11,707; 95% CI: 4.9 to 9.8).

There was a regional difference in the number of injections that were administered per year. The mean injections administered per year was 4.3 (95% CI: 3.5 to 5.1), 5.6 (95% CI: 4.8 to 6.4), 6.1 (95% CI: 5.3 to 6.9), and 7.7 (95% CI: 5.9 to 9.5) in continental Europe (n = 10,748), United Kingdom (n = 12,886), North America (n = 703), and Australia (n = 1,334) respectively.

Patients receiving the PRN regimen received a mean of 4.7 injections (95% CI: 4.0 to 5.5) and 8.8 (95% CI: 7.4 to 10.3) visits per year, with 5.4 (95% CI: 4.1 to 6.8) injections given in the first year (n = 20,313), 3.7 (95% CI: 1.8 to 5.5) injections in the second year (n = 14,184), and 2.8 (95% CI: 0.0 to 6.8) injections in the third year (n = 11,714). These patients had 8.6 (95% CI: 6.8 to 10.3) visits in the first year (n = 14,171), 9.2 (95% CI: 4.4 to 14.0) visits in the second year (n = 12,557), and 8.2 (95% CI: 0.0 to 17.5) visits on average per year in subsequent years (n = 11,403).

Patients on the treat-and-extend regimen received significantly more injections (6.9; 95% CI: 5.6 to 8.2) and had fewer visits (7.6; 95% CI: 5.9 to 9.3) per year compared with patients on PRN ($P < 0.001$ and $P <$

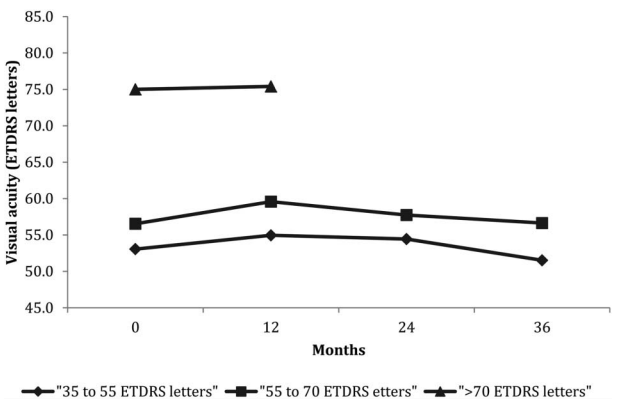

Fig. 1. Mean VA at baseline and year 1, 2, and 3 or more in 3 initial VA groups.

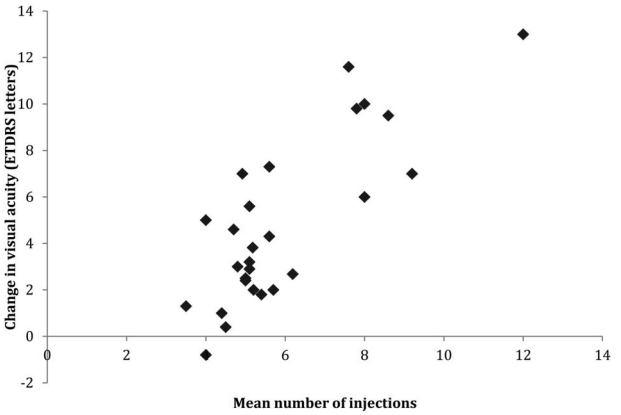

Fig. 2. Mean change in VA versus the mean number of injections administered, in the first year of treatment of included studies.

0.001, respectively; mixed-effects models). These patients received 7.3 (95% CI: 5.9to 8.6) injections in the first year (n = 2,458), 4.9 (95% CI: 3.3 to 6.5) injections in the second year (n = 2,521), and 4.0 (95% CI: 0.0 to 8.9) injections in the third year (n = 1,390). They also visited their ophthalmologist 7.8 (95% CI: 5.5 to 10.1) times in the first year (n = 361), then 7.6 (95% CI: 4.6 to 10.7) times in the second year (n = 424), and 7.0 (95% CI: 1.2 to 12.8) times on average per year in the subsequent years (n = 304).

There was a significant reduction in injections from years 1 and 2 for treat-and-extend and PRN ($P = 0.011$ and $P = 0.046$, respectively; metaregression on mean differences) but not between years 2 and 3 ($P = 0.667$ and $P = 0.514$, respectively). There was no significant change in the number of visits from year to year for both treat-and-extend and PRN.

Dose of Ranibizumab Used

A few studies used a treatment dosage that differed from the standard 0.5 mg of ranibizumab. Michalova et al[18] used 0.3-mg ranibizumab until April 2007 when the dosage was changed to 0.5 mg, whereas Hjelmqvist et al[19] used 0.23 mg ranibizumab in their study. Data from Hjelmqvist et al[19] were removed from our analysis as it was based solely on a nonstandard dose.

Also, Gupta et al[20] did not comment on the dose that they administered and it was therefore assumed that they used a dose of 0.5 mg, which is licensed in the United States for nAMD where the study is based.

Safety Outcomes

There were 648 adverse events reported in total, with 17 cases of endophthalmitis, 41 patients developing cerebrovascular accident and acute coronary syndrome, and 36 deaths. Many of the included observational studies did not include sufficient data on safety outcomes (Table 3).

Heterogeneity

The amount of heterogeneity (I^2) in each of the outcome measures was >95%. The R^2 value for region was ~25% for baseline age, baseline VA, and mean injections received per year. The R^2 value for regimen was ~30% for VA change.

Discussion

This metaanalysis of real-world observational studies of intravitreal ranibizumab therapy for nAMD demonstrates successful prevention of severe visual loss. The degree of improvement in VA was greatest in the first year of treatment; however, the initial gain was not always maintained, with a gradual decline observed in the second and subsequent years. Patients receiving a treat-and-extend regimen also had better VA outcomes with more injections and fewer visits than those receiving PRN treatment.

There was an association between observed VA outcomes and injection frequency, which was also reflected in the regional variation in the initial gain in VA and maintenance of this improvement over time. In the first year of treatment, the mean number of intravitreal ranibizumab injections reported in studies from continental Europe (4.3), United Kingdom (5.6), North America (6.1), and Australia (7.7), correlated with the mean gain in VA, +3.1, +2.5, +6.0 and +7.8 ETDRS letters, respectively. A greater gain in VA in the first year of treatment was therefore generally observed in regions that administered more intravitreal ranibizumab injections. There was also less loss of vision from the second year onwards in patients receiving a greater number of injections. This association may therefore suggest that the frequency of injections could be an important independent indicator of improvement in VA outcomes.

Alternatively, it is possible that the observed results may be caused by underlying differences in the populations rather than the frequency of injections administered, considering that the baseline VA of these regions ranged from 47.4 to 57.8 ETDRS letters (6/38 to 6/19 Snellen equivalents).

The amount of heterogeneity in each of the outcome measures was substantial ($I^2 > 95\%$). For baseline age, baseline VA, and mean injections received per year, ~25% of this heterogeneity can be attributed to the study region. A third of the heterogeneity in VA change between studies can be explained by the treatment regimen (33.8% of the heterogeneity for the first year and 30.9% for the second). Study region explains much less for this outcome. However, the pseudo R^2 statistic can be very imprecise particularly if the number of studies is small (or the number of studies per grouping variable is small).[55]

There was a large variation in VA outcomes across countries. Having said this, the confounding effect of restrictions on intravitreal therapy put in place by the local healthcare systems must be taken into account. For instance, PRN was used in the United Kingdom, whereas treat-and-extend was used in Australia. The local healthcare system is therefore important to consider when interpreting VA outcomes.

The mean baseline VA was strongly correlated with long-term visual outcome. Therefore, it is important to have systems in place to identify nAMD and commence treatment early. Patients are more likely to

retain vision sufficient for maintaining a driving license and high level of independence with early treatment. Restrictions on therapy for patients with nAMD with VA better than 20/30, as mandated by organizations such as National Institute for Health and Care Excellence in the United Kingdom, may adversely affect a group that is most likely to benefit from treatment.[56]

This metaanalysis also provides insight into what is achievable in real-life clinical practice when compared with Phase 3 studies. The whole cohort of patients in this metaanalysis gained a mean 5.0 ETDRS letters after 12 months of ranibizumab therapy with a mean number of 5.4 injections and 8.3 visits per year. In contrast, the mean gain in VA after 12 months of 0.5 mg ranibizumab therapy was 7.2 ETDRS letters in the MARINA trial and 11.3 ETDRS letters in the ANCHOR trial, based on 12 injections and 12 follow-up examinations over the course of a year. Hence, comparing our metaanalysis with Phase 3 clinical trials shows that, on the whole, patients receive fewer injections and visits in real-world practice and obtain a lower initial gain in VA after 12 months of intravitreal ranibizumab therapy.

The proportion of arterial thromboembolic events or death in this metaanalysis were 0.6% (n = 41) and 0.7% (n = 36), respectively. These numbers were generally lower than in Phase 3 clinical trials, with the ANCHOR trial reporting proportions of 2.7% and 1.4%, respectively, whilst in the MARINA trial these proportions were 3.8% and 2.6%, respectively. Nonetheless, it is likely that the lower numbers reported in real-world observational studies represent incomplete capture of systemic safety data.

The multicenter and observational nature of the included studies was both a strength and limitation in this metaanalysis. The large pooled population of patients from multiple centers and countries provided data that served as a real-life standard to which local outcomes can be compared. These observational studies also provide valuable information on how the results from Phase 3 clinical trials may translate to the wider population in which the stringent inclusion and exclusion criteria of the clinical trials no longer apply.

However, they are also a few limitations as clinical protocols such as dosing may change over time and the data depend on the documentation protocols and management criteria followed by each center, which may have varied. The rate of patients who had an arterial thromboembolic event or death per year could not be calculated because of the variation in the collection of safety data across studies. The VA was also measured in a standard clinical setting rather than the more accurate but time-consuming best-corrected VA measurements performed in a clinical trial setting. It is also possible that the baseline characteristics of study populations of different included studies were not similar. For instance, nAMD is being identified and treated earlier in its disease course as anti-vascular endothelial growth factor treatment becomes more widespread. More recent studies are therefore more likely to include eyes that are healthier than older studies, which has implications for the results obtained.

This metaanalysis has also highlighted the need for a standardized framework to collect outcome data of efficacy and safety of intravitreal ranibizumab for nAMD. For instance, the International Consortium for Health Outcomes Measurements (ICHOM) has a global standard set of outcome measures for macular degeneration based on consensus of international experts.[57] A standardized framework would facilitate a more consistent and accurate collection of clinically meaningful data and make it easier to compare outcomes. The collection of large amounts of data on the treatment of nAMD in routine practice can also be achieved using programs such as Medisoft or web-based tools developed in the Fight Retinal Blindness! Project, which helps to consolidate records from multiple sites and ophthalmic instruments.[58] Addressing this issue will allow us to evaluate new treatments as they are introduced into real-world practice in a more timely manner than large prospective Phase 4 studies.

In conclusion, patients who received intravitreal ranibizumab therapy in real-world clinical practice for nAMD were, in general, protected against severe vision loss. However, the included observational studies did not report the same magnitude of VA improvement as Phase 3 clinical trials and these VA improvements were not maintained in the long term, particularly with treatment regimens that had low injection frequency. More research is warranted using standardized data collection methods to allow easier comparison of efficacy and safety outcomes to improve standards globally.

Key words: age-related macular degeneration, neovascular, observational, ranibizumab, real-world outcomes.

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